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Intraventricular Thrombus Formation and Embolism in Takotsubo Syndrome: Insights From the International Takotsubo Registry

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Abstract: OBJECTIVE Takotsubo syndrome (TTS) is characterized by acute left ventricular dysfunction, which can contribute to intraventricular thrombus and embolism. Still, prevalence and clinical impact of thrombus formation and embolic events on outcome of TTS patients remain unclear. This study aimed to investigate clinical features and outcomes of patients with and without intraventricular thrombus or embolism. Additionally, factors associated with thrombus formation or embolism, as well as predictors for mortality, were identified. Approach and Results: TTS patients enrolled in the International Takotsubo Registry at 28 centers in Australia, Europe, and the United States were dichotomized according to the occurrence/absence of intraventricular thrombus or embolism. Patients with intraventricular thrombus or embolism were defined as the ThrombEmb group. Of 1676 TTS patients, 56 (3.3%) patients developed intraventricular thrombus and/or embolism following TTS diagnosis (median time interval, 2.0 days [range, 0-38 days]). Patients in the ThrombEmb group had a different clinical profile including lower left ventricular ejection fraction, higher prevalence of the apical type, elevated levels of troponin and inflammatory markers, and higher prevalence of vascular disease. In a Firth bias-reduced penalized-likelihood logistic regression model apical type, left ventricular ejection fraction 30%, previous vascular disease, and a white blood cell count on admission $>10\times10^3$ cells/ L emerged as independent predictors for thrombus formation or embolism. CONCLUSIONS Intraventricular thrombus or embolism occur in 3.3% of patients in the acute phase of TTS. A simple risk score including clinical parameters associated with intraventricular thrombus formation or embolism identifies patients at increased risk. CLINICAL TRIAL REGISTRATION URL: http://www.clinicaltrials.gov. Unique identifier: NCT01947621.

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Arteriosclerosis, Thrombosis, and Vascular Biology

CLINICAL AND POPULATION STUDIES

Intraventricular Thrombus Formation and Embolism in Takotsubo Syndrome

Insights From the International Takotsubo Registry

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OBJECTIVE: Takotsubo syndrome (TTS) is characterized by acute left ventricular dysfunction, which can contribute to intraventricular thrombus and embolism. Still, prevalence and clinical impact of thrombus formation and embolic events on outcome of TTS patients remain unclear. This study aimed to investigate clinical features and outcomes of patients with and without intraventricular thrombus or embolism. Additionally, factors associated with thrombus formation or embolism, as well as predictors for mortality, were identified.

APPROACH AND RESULTS: TTS patients enrolled in the International Takotsubo Registry at 28 centers in Australia, Europe, and the United States were dichotomized according to the occurrence/absence of intraventricular thrombus or embolism. Patients with intraventricular thrombus or embolism were defined as the ThrombEmb group. Of 1676 TTS patients, 56 (3.3%) patients developed intraventricular thrombus and/or embolism following TTS diagnosis (median time interval, 2.0 days [range, 0–38 days]). Patients in the ThrombEmb group had a different clinical profile including lower left ventricular ejection fraction, higher prevalence of the apical type, elevated levels of troponin and inflammatory markers, and higher prevalence of vascular disease. In a Firth bias-reduced penalized-likelihood logistic regression model apical type, left ventricular ejection fraction ≤30%, previous vascular disease, and a white blood cell count on admission >10×10^3 cells/μL emerged as independent predictors for thrombus formation or embolism.

CONCLUSIONS: Intraventricular thrombus or embolism occur in 3.3% of patients in the acute phase of TTS. A simple risk score including clinical parameters associated with intraventricular thrombus formation or embolism identifies patients at increased risk.

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Key Words: embolism ■ outcome ■ risk score ■ Takotsubo syndrome ■ thrombus

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Nonstandard Abbreviations and Acronyms

CRP	C-reactive protein
HR	hazard ratio
InterTAK registry	International Takotsubo registry
LV	left ventricular
LVEF	left ventricular ejection fraction
ThrombEmb	thrombotic or embolic event
TTS	takotsubo syndrome
WBC	white blood cell count

Highlights

- Thrombus formation and embolic events occur in ≈3% of patients with takotsubo syndrome.
- The International Takotsubo Thrombus Risk Score presents a valuable tool to identify patients at risk for thrombus formation or embolism.

Takotsubo syndrome (TTS) is increasingly being recognized as an important differential diagnosis in patients presenting with acute chest pain or heart failure symptoms.[1–6] Although initially considered as rather benign condition, TTS is associated with substantial morbidity and mortality.[1,7–11] Indeed, severe in-hospital complications including arrhythmias,[12] left ventricular (LV) outflow tract obstruction,[13] cardiogenic shock,[14] LV rupture,[15] and death[1] were reported, and rates of adverse events are comparable to those of patients with acute coronary syndromes.[1,7] Case reports and small observational studies have pointed toward the occurrence of thromboembolic complications in TTS patients.[16–21] These studies reported a wide ranging prevalence of 2.2% to 12.2% for thrombus formation and embolism,[22,23] but the sequel of thrombus or embolic events associated with TTS are uncertain and have not yet been investigated in a large patients' cohort.

The aim of the present study was, therefore, to assess the prevalence, clinical correlates, and outcomes of patients with intraventricular thrombus or embolism in TTS using data from the International Takotsubo (InterTAK) Registry (www.takotsubo-registry.com).

MATERIALS AND METHODS

The design of the InterTAK Registry has previously been described elsewhere.[1,24] One thousand six hundred seventy-six patients were selected for the present study according to availability of comprehensive imaging data regarding the presence or absence of intraventricular thrombus or embolism. TTS was defined based on InterTAK Diagnostic Criteria.[6] The authors declare that all supporting data are available within the article and its online-only Data Supplement.

Data on demographic characteristics, clinical presentation, triggering factors, admission and discharge medication, comorbidities (including vascular disease such as stroke or transient ischemic attack, myocardial infarction, peripheral artery disease, or aortic plaque), laboratory values, electrographic abnormalities, and imaging findings (echocardiography, coronary angiography, ventriculography, and cardiac magnetic resonance imaging [MRI]) along with short- and long-term outcomes were collected. In-hospital complications were defined as a composite of cardiogenic shock, ventricular tachycardia, and death. Follow-up was conducted through telephone interviews, clinical visits, or perusal of medical records.[1,2] The median follow-up time was 169 days (interquartile range, 8–1041 days).

TTS patients were dichotomized according to the presence or absence of intraventricular thrombus or embolism. Patients in whom a preceding TTS event could be identified as the etiological cause of thrombus formation or embolism were defined as the ThrombEmb group (consisting of left or right ventricular thrombus formation, ischemic stroke, splenic infarction, or coronary embolus). In cases in which acute stroke preceded the TTS event, stroke was defined as a physical triggering factor, and these cases were not included in the ThrombEmb group. Furthermore, patients with atrial fibrillation who had an embolic event were excluded from the study since it cannot be determined whether the embolism was due to atrial fibrillation or TTS. For the diagnosis of ventricular thrombus, established criteria were applied.[25] Clinical characteristics and outcomes were compared between groups, and risk factors for thrombus formation or embolism, as well as predictors of 6-month mortality, were identified. In addition, a subanalysis to assess differences in the clinical profile and outcomes of TTS patients with ventricular thrombus and TTS patients with embolism was conducted.

Statistical Analysis

Continuous variables are given as mean±SD or median with interquartile range and were tested for differences with the Student *t* test or Mann-Whitney *U* test. Categorical variables are summarized as frequencies and percentages and were analyzed using Pearson χ^2 test or Fisher exact test.

Clinical variables that were significantly different at baseline comparison between groups and might have an impact on thrombus formation were included in Firth bias-reduced penalized-likelihood logistic regression model[26,27] to identify clinical parameters independently associated with thrombus formation or embolic events. Firth logistic regression has become a standard approach to the problem of separation in logistic regression with rare events. It is defined by $\log L^{*}(\beta)=\log L(\beta)+A(\beta)$ with $A(\beta)=1/2\log\det(I(\beta))$ where $I(\beta)$ is the Fisher information matrix and $L(\beta)$ is the likelihood.[28] Two simple modifications of Firth logistic regression resulting in unbiased predicted probabilities were given by Puhr et al.[27] The first corrects the predicted probabilities by a post hoc adjustment of the intercept. The other is based on an alternative formulation of Firth penalization as an iterative data augmentation procedure.

A prognostic index (InterTAK Thrombus Prognostic Index) and a risk score (InterTAK Thrombus Risk Score) were calculated using the coefficients of Firth logistic regression model. The coefficients were transformed into item scores and added up to a total score, the InterTAK Thrombus Prognostic Index. The item scores

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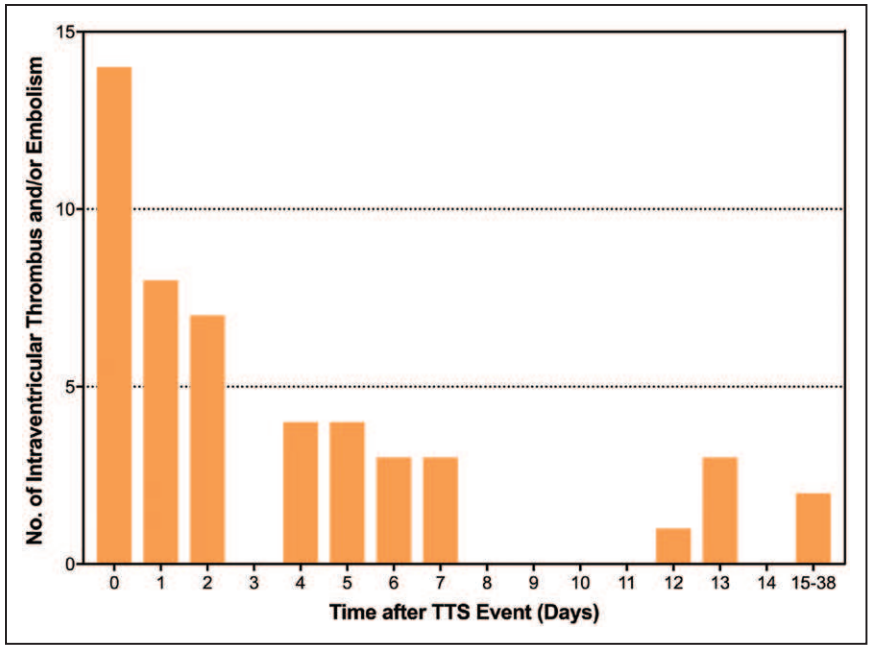

Figure 1. Temporal occurrence of intraventricular thrombus or embolism in takotsubo syndrome (TTS).

were calculated by dividing each coefficient with the smallest coefficient in the model and then by rounding to the nearest 0.5. Internal validation was performed using 500 bootstrapping samples. The InterTAK Thrombus Prognostic Index was divided into different risk groups with respect to optimal cutoffs that form the InterTAK Thrombus Risk Score. Missing values were replaced by multiple imputation before logistic regression with Firth bias correction. To assess the impact of thrombotic or embolic events on 6-month mortality, a Cox-regression analysis was executed including parameters that had statistical significance at baseline comparison. Hazard ratios (HRs) are reported with 95% CIs.

A 2-sided *P* of <0.05 was considered to indicate statistical significance. Statistical analysis was performed using IBM SPSS Statistics, version 24.0 and 25.0 (IBM Corp, Armonk, NY), and R, version 3.5.1 (R Foundation), and graphs were generated using Prism 8 (GraphPad, La Jolla, CA).

RESULTS

Study Population

Overall, 1676 patients were included in the present study. The clinical course was complicated by intraventricular thrombus or embolism in 56 patients (3.3%) at a median time interval of 2.0 days (range, 0–38 days) following TTS event (Figure 1). Among the 56 patients, 38 (67.9%) had ventricular thrombus of whom 36 (64.3%) had LV thrombus, 1 (1.8%) had right ventricular thrombus, and 1 (1.8%) had LV and right ventricular thrombus. Furthermore, 13 (23.2%) had ischemic stroke, and 1 (1.8%) had coronary thrombus. In 4 patients (7.2%), thrombus formation or thrombus was observed in >1 location. As such, 1 (1.8%) had ischemic stroke and splenic infarction, and 3 (5.4%) patients had LV thrombus and ischemic stroke (Figure 2). A detailed description on the occurrence and type of embolic events is presented in Figure I in the online-only Data Supplement.

Clinical, laboratory, and electrocardiographic characteristics are shown in Table 1. Age, sex, and prevalence of triggering factors did not differ between the ThrombEmb and the non-ThrombEmb groups. Patients in the ThrombEmb group more frequently presented with the apical TTS type (91.1% versus 70.1%; *P*<0.001).

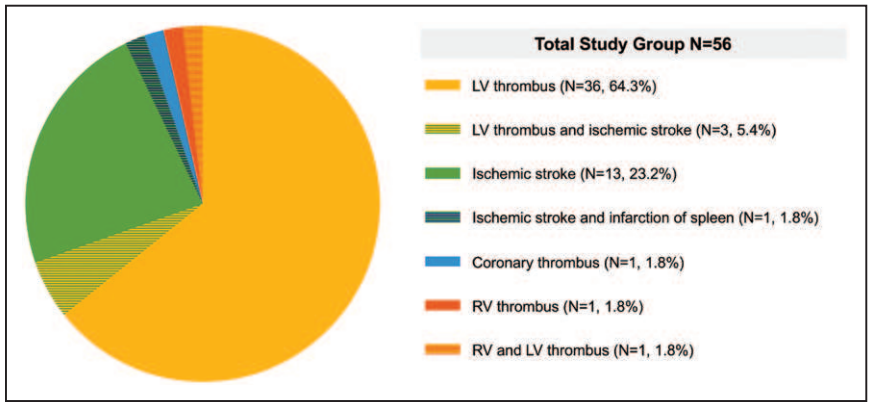

Figure 2. Of 1676 patients studied, 56 had thrombotic or embolic events, 38 patients had ventricular thrombi, and 13 patients had embolism.
In 5 patients, thrombotic or embolic events were observed in >1 location (shaded areas). LV indicates left ventricle; and RV, right ventricle.

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Table 1. Characteristics of Patients

Characteristics	ThrombEmb Group (n=56)	Non-ThrombEmb Group (n=1620)	*P* Value
Demographics			
Female sex, n/total n (%)	47/56 (83.9)	1463/1620 (90.3)	0.12
Age, y	67.0±13.4 (n=56)	67.1±12.8 (n=1620)	0.96
Body mass index, kg/m^2	25.3±5.8 (n=38)	25.1±5.4 (n=1201)	0.99
Triggers, n/total n (%)			
Physical trigger	27/56 (48.2)	602/1620 (37.2)	0.09
Emotional trigger	12/56 (21.4)	486/1620 (30.0)	0.17
Both emotional and physical trigger	3/56 (5.4)	119/1620 (7.3)	0.79
No evident trigger	14/56 (25.0)	413/1620 (25.5)	0.93
Takotsubo type, n/total n (%)			
Apical type	51/56 (91.1)	1135/1620 (70.1)	<0.001
Cardiac biomarkers, median (IQR)			
Troponin on admission, multiple of ULN*	16.75 (4.27–44.60), n=45	8.04 (2.68–22.34), n=1305	0.028
Troponin maximum, multiple of ULN*	27.36 (9.00–80.00), n=47	13.73 (5.13–35.78), n=1354	0.004
Creatine kinase on admission, multiple of ULN	0.73 (0.49–1.50), n=34	0.87 (0.54–1.41), n=1150	0.93
Creatine kinase maximum, multiple of ULN	1.11 (0.73–1.98), n=35	1.11 (0.65–1.97), n=1189	0.47
BNP on admission, multiple of ULN†	7.88 (3.02–12.86), n=17	6.20 (2.22–16.74), n=467	0.66
BNP maximum, multiple of ULN†	11.68 (5.69–29.28), n=26	10.09 (4.53–24.37), n=601	0.41
Inflammatory markers, median (IQR)			
CRP on admission, mg/L	6.55 (3.12–22.68), n=32	3.80 (1.30–11.98), n=1039	0.014
CRP maximum, mg/L	22.45 (4.18–133.98), n=36	8.90 (2.70–41.47), n=1140	0.017
WBC on admission, 10^3/μL	11.50 (9.90–16.10), n=47	9.67 (7.47–12.55), n=1402	<0.001
WBC maximum, 10^3/μL	12.70 (10.60–18.20), n=51	10.50 (8.20–13.56), n=1442	<0.001
Lipid status, median (IQR)			
Triglyceride, mmol/L	1.33 (1.00–1.62), n=23	1.11 (0.83–1.60), n=856	0.29
Cholesterol, mmol/L	4.74 (3.70–5.44), n=23	4.80 (3.94–5.57), n=869	0.57
HDL cholesterol, mmol/L	1.31 (1.12–1.51), n=20	1.45 (1.14–1.80), n=758	0.25
LDL cholesterol, mmol/L	3.02 (2.41–3.65), n=16	2.70 (2.00–3.40), n=717	0.27
ECG on admission, n/total n (%)			
Atrial fibrillation	5/46 (10.9)	87/1425 (6.1)	0.20
ST-segment elevation	22/46 (47.8)	591/1425 (41.5)	0.39
QTc, ms	460.4±43.6 (n=34)	458.3±47.6 (n=1150)	0.58
Hemodynamics, mean±SD (n)			
Heart rate, bpm	96.2±20.5 (n=40)	87.1±21.8 (n=1246)	0.005
Systolic blood pressure, mm Hg	130.5±27.5 (n=43)	130.8±28.4 (n=1267)	0.92
Diastolic blood pressure, mm Hg	76.6±13.8 (n=42)	76.4±16.8 (n=1241)	0.85
LVEF, %‡	38.3±12.1 (n=47)	40.9±11.6 (n=1446)	0.043
Coexisting medical condition, n/total n (%)			
Hypertension	32/55 (58.6)	1067/ 1590 (67.1)	0.17
Diabetes mellitus	4/55 (7.3)	256/1604 (16.0)	0.08
Current smoking	10/51 (19.6)	311/1525 (20.4)	0.89
Hypercholesterolemia	13/55 (23.6)	516/1559 (33.1)	0.14
Positive family history	6/41 (14.6)	272/1361 (20.0)	0.40
Previous vascular disease§	19/49 (38.8)	218/1478 (14.7)	<0.001
Stroke or TIA	10/51 (19.6)	103/1484 (6.9)	0.003
PAD or aortic plaques	6/53 (11.3)	54/1612 (3.3)	0.010
Myocardial infarction	6/54 (11.1)	74/1576 (4.7)	0.05
Cancer (total)	14/53 (26.4)	244/1507 (16.2)	0.049

(*Continued*)

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Table 1. Continued

Characteristics	ThrombEmb Group (n=56)	Non-ThrombEmb Group (n=1620)	*P* Value
Medication on admission, n/total n (%)			
ACE inhibitor or ARB	17/38 (44.7)	504/1301 (38.7)	0.46
β-Blocker	15/38 (39.5)	407/1301 (31.3)	0.28
Calcium-channel antagonist	1/37 (2.7)	99/1295 (7.6)	0.52
Statin	6/37 (16.2)	264/1295 (20.4)	0.53
Aspirin	14/37 (37.8)	451/1295 (34.8)	0.71
ADP antagonist	9/37 (24.3)	102/1295 (7.9)	0.002
Anticoagulants	0/37 (0.0)	54/1295 (4.2)	0.40

ACE indicates angiotensin-converting-enzyme; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CRP, C-reactive protein; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; PAD, peripheral artery disease; QTc, QT interval corrected for heart rate; ThrombEmb, thrombotic or embolic event; TIA, transient ischemic attack; ULN, upper limit of the normal range; and WBC, white blood cell count.

*Including upper limits of the normal range for troponin T, high-sensitivity troponin T, and troponin I.

†Including upper limits of the normal range for brain natriuretic peptide and the N terminus of prohormone brain natriuretic peptide.

‡Data obtained during catheterization or echocardiography; if both results were available, data from catheterization were used.

§Composite of history of stroke/TIA, PAD, aortic plaques, or myocardial infarction.

Cardiac troponin levels on admission and peak troponin levels were significantly higher in the ThrombEmb as compared with the non-ThrombEmb group (Table 1). White blood cell count (WBC) counts on admission and corresponding peak WBC were also increased in the ThrombEmb group. Similarly, CRP (C-reactive protein) levels on admission and corresponding peak CRP levels were higher in the ThrombEmb group (Table 1).

Compared with patients in the non-ThrombEmb group, patients in the ThrombEmb group had a higher heart rate (96.2±20.5 bpm versus 87.1±21.8 bpm; *P*=0.005). There were no significant differences between the 2 groups in terms of the prevalence of ST-segment elevation or QTc prolongation. LV ejection fraction (LVEF) on admission (38.3±12.1% versus 40.9±11.6%; *P*=0.043) was lower in the ThrombEmb group compared with the non-ThrombEmb group. Patients in the ThrombEmb group had a higher prevalence of prior vascular disease (ie, transient ischemic attack/stroke, myocardial infarction, peripheral artery disease, or aortic plaques; 38.8% versus 14.7%; *P*<0.001). Cardiovascular medications on admission were balanced between groups and none of the patients in the ThrombEmb group was admitted with oral anticoagulants compared with 4.2% in the non-ThrombEmb group (*P*=0.40).

A subanalysis comparing TTS patients with ventricular thrombus and embolism demonstrated no differences in clinical features and outcomes. At discharge, patients with ventricular thrombus received more frequently anticoagulants compared with patients with embolism (70.6% versus 26.7%; *P*=0.004; Table I in the online-only Data Supplement; Figure II in the online-only Data Supplement).

Clinical Parameters Associated With Thrombus Formation or Embolism—the InterTAK Thrombus Risk Score

In a multivariate penalized maximum likelihood estimation analysis, apical TTS, previous vascular disease, LVEF ≤30%, and WBC on admission >10×10^3 cells/μL emerged as independent predictors of thrombus formation. An internal validation with 500 bootstrap samples showed that the results are stable and reliable with the following β-coefficients: apical TTS (1.13 [95% CI, 0.32–2.15]; *P*=0.005), previous vascular disease (1.31 [95% CI, 0.73–1.87]; *P*<0.001), LVEF ≤30% (1.10 [95% CI, 0.55–1.65]; *P*<0.001), and first WBC >10×10^3 cells/μL (0.78 [95% CI, 0.20–1.39]; *P*=0.007).

The C index of Firth penalized maximum likelihood estimation as a measure of goodness of fit for thrombotic or embolic event is 0.77 ([95% CI, 0.72–0.84]; *P*<0.001). The item scores of the InterTAK Prognostic Index (Figure 3A and 3B) based on the 4 significant coefficients are defined as follows: 1.5 points for apical TTS, 1.5 points for prior vascular disease, 1.5 points for LVEF ≤30%, and 1 point for WBC on admission >10×10^3 cells/μL. The InterTAK Prognostic Index for a patient is the sum of the corresponding item scores (minimum, 0; maximum, 5.5). An optimal cutoff value of the score is 3 dividing the patients into low (≤3) and high risk (>3) forming the corresponding risk score. Of the TTS patients, 83.1% were in the low- and 16.9% in the high-risk group. Of the low-risk patients, 1.7% and 11.3% of the high-risk patients had a thrombotic or embolic event. None of the patients with 0 score points (n=204, 12.2%) had an event but 15.6% of patients with 5.5 score points (n=32). Furthermore, only 2 (0.5%) of 421 patients with LVEF >30% and atypical TTS had a thrombotic or embolic event. The corresponding area under the ROC curve is 0.78 with SE of 0.030 and asymptotic 95% CI of 0.72–0.83; *P*<0.001.

Clinical Outcomes

Rates of in-hospital complications (22.2% versus 12.6%; *P*=0.039) such as cardiogenic shock (17.9% versus 9.6%; *P*=0.040) were higher in the ThrombEmb group as

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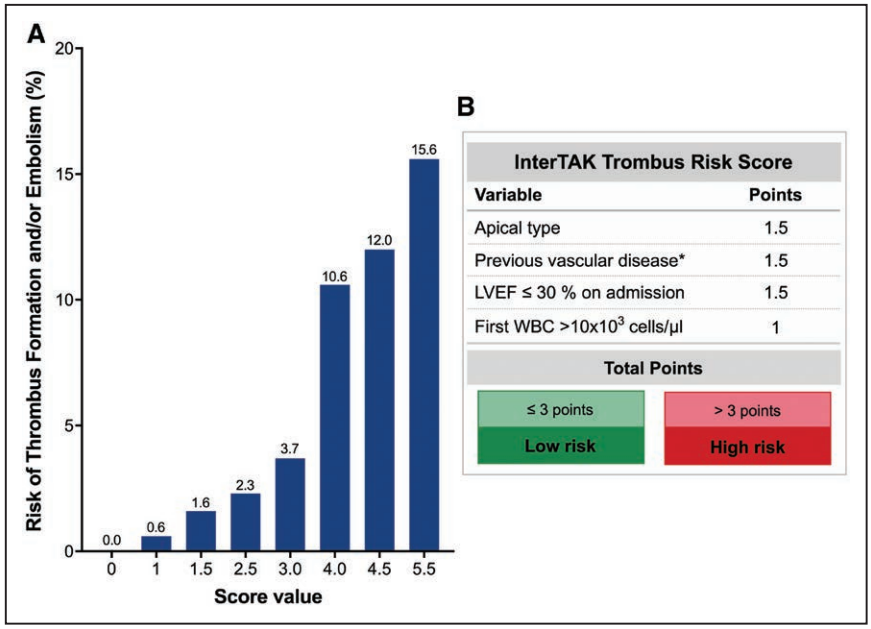

Figure 3. InterTAK Thrombus Risk Score.
A, International Takotsubo (InterTAK) prognostic index showing a progressive increase in risk with increasing score points. **B**, Variables included in the InterTAK Thrombus Risk Score. A cutoff of 3 classifies patients in low- and high-risk categories.LVEF indicates left ventricular ejection fraction; and WBC, white blood cell.

compared with the non-ThrombEmb group. Furthermore, patients in the ThrombEmb group required more often acute cardiac care measures (35.7% versus 20.4%; *P*=0.005) such as invasive or noninvasive ventilation (30.4% versus 17.1%; *P*=0.010) as well as catecholamine administration (23.2% versus 12.7%; *P*=0.021; Table 2). At multivariable Cox-regression analysis, LVEF ≤30% (HR, 2.72 [95% CI, 1.88–3.95]; *P*<0.0001), heart rate >94bpm (HR, 1.73 [95% CI, 1.19–2.52]; *P*=0.004), first WBC >10×10^3 cells/µL (HR, 2.05 [95% CI, 1.39–3.03]; *P*<0.001), and cancer (HR, 1.96 [95% CI, 1.32–2.87]; *P*=0.001) emerged as independent predictors of 6-months mortality (Figure III in the online-only Data Supplement).

DISCUSSION

This study analyzed the prevalence, clinical correlates, and outcomes of intraventricular thrombus or embolism in a large cohort of patients with TTS. The main findings are: (1) Intraventricular thrombus and/or embolism occur with a prevalence of 3.3%; (2) intraventricular thrombus are associated with clinically relevant embolic events in different organs; (3) intraventricular thrombus and embolic events occur at a median time interval of 2 days after TTS; (4) the apical form of TTS, severe LV systolic dysfunction prior vascular disease and an elevated WBC are clinical parameters associated with intraventricular thrombus formation and/or embolic events in TTS.

Thromboembolic events may complicate the course following a TTS, particularly during the acute phase when LV function is still depressed. Besides blood stasis due to myocardial stunning and regional hypo-/akinesia, endothelial activation and systemic hypercoagulability may promote thrombus formation in TTS patients.[29] Patients presenting with the typical form of TTS seem to be particularly vulnerable to ventricular thrombus formation, probably owing to the larger amount of myocardium affected

Table 2. Complications and Acute Treatment

Characteristics	ThrombEmb Group (n=56)	Non-ThrombEmb Group (n=1620)	*P* Value
In-hospital complications, n/total n (%)	12/54 (22.2)	198/1569 (12.6)	0.039
Cardiogenic shock	10/56 (17.9)	154/1611 (9.6)	0.040
Ventricular tachycardia	4/54 (7.4)	40/1563 (2.6)	0.06
Death	4/56 (7.1)	73/1620 (4.5)	0.32
Acute cardiac care treatment, n/total n (%)	20/56 (35.7)	328/1611 (20.4)	0.005
Intra-aortic balloon pump	4/56 (7.1)	39/1611 (2.4)	0.053
Invasive or noninvasive ventilation	17/56 (30.4)	275/1612 (17.1)	0.010
Cardiopulmonary resuscitation	4/56 (7.1)	94/1620 (5.8)	0.57
Catecholamine use	13/56 (23.2)	204/1612 (12.7)	0.021

ThrombEmb indicates thrombotic or embolic event.

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and the more pronounced reduction of LV systolic function observed during the acute phase. A recent study found a LV thrombus prevalence of 2.2% in TTS with all thrombus events occurring in apical TTS cases, corroborating the association between apical TTS and thrombus formation.[23] Similarly, LV thrombus formation following an acute myocardial infarction is mainly observed when the anterior LV wall is affected.[30–32]

The relation between stroke and TTS is complex as it may both be a trigger and a complication of this condition; indeed, neurological events such as ischemic stroke may induce an acute TTS episode,[33–35] but may also complicate the course of TTS as observed in this study. Whether cardio-embolism represents the predominant cause of ischemic stroke in TTS patients or whether other mechanisms may also be involved such as cerebral vasospasm remains to be determined.

Interestingly, inflammatory biomarkers were significantly elevated in TTS patients with thrombotic or embolic complications. Although this might be an epiphenomenon as embolic occlusion of a major artery with tissue ischemia and necrosis may itself activate inflammatory pathways, cytokines released from WBCs can promote or maintain thrombus formation in TTS. Indeed, interleukins, tumor necrosis factor alpha and other inflammatory molecules induce tissue factor expression in endothelial cell thereby activation the coagulation cascade.[36] In line with this interpretation, increased CRP levels and WBC have been linked to LV thrombus formation also in patients with large anterior myocardial infarction.[37]

Results of the multivariable Cox-regression suggest that the higher rate of adverse events in patients is attributed to clinical parameters such as LVEF ≤30%, heart rate >94bpm, first WBC count >10×10^3 cells/μL, and malignancies and not to the thrombotic and/or embolic event per se.

The recent literature offers little guidance for the management of TTS patients with intraventricular thrombus as randomized trials are lacking. Given the potential complications which can be associated with thrombotic or embolic events early diagnosis is important to assure optimal medical care. Importantly, our study provides a useful risk stratification tool which may assist in the identification of patients at increased thrombotic and/or embolic risk and in need for intense monitoring and follow-up. The proposed risk score, including the 4 variables apical form of TTS, severe LV systolic dysfunction, elevated WBC levels and prior vascular disease has the advantage of providing an easy applicable bedside test. Close monitoring may include serial echocardiography to detect clinically silent ventricular thrombus formation before devastating embolic complications, particularly during the first days following the acute TTS event when the risk appears to be highest. Contrast echocardiography and cardiac MRI are sensitive methods to detect ventricular thrombus and may be considered in patients with a high-risk score. In the presence of LV thrombus anticoagulation therapy might be considered on an individual basis.

Limitations

Some limitations need to be considered. First, this study has the limitations inherent to an observational and partly retrospective registry. Second, intraventricular thrombus formation or embolic events were not prespecified variables, and diagnosis was based on patient records and different imaging modalities including transthoracic echocardiography and cardiac MRI. Furthermore, systematic MRI assessment was not performed in all patients since data went back to 1998 where MRI was not broadly and systematically available. Third, as the InterTAK Registry is an observational study, no fixed imaging time points were set. Therefore, the impact of timing on the diagnosis of ventricular thrombi remains unclear. The real prevalence of ventricular thrombi might be higher than the one reported herein if clinically silent thrombi remained undetected.

Conclusions

Intraventricular thrombus and embolism occur in 3.3% of patients with TTS during the acute phase. A simple bedside risk score including clinical parameters associated with intraventricular thrombus formation and embolism such as the apical TTS, low LVEF. Prior vascular disease and elevated WBC improves the thrombotic risk assessment in TTS patients. Patients in the high-risk group may benefit from a more intense follow-up.

ARTICLE INFORMATION

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